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Serial No. 09/402,273

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In Re Application of:
Jorj Terry ULRICH et al.

Confirmation No. 5731

Serial No. 09/402,273

Group Art Unit 1644

Filing Date: December 13, 1999

Examiner Phuong N. HUNYH

Title: ALLERGEN FORMULATION

APPEAL BRIEF

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APPEAL BRIEF

Pursuant to 35 U.S.C. § 134(a) and 37 C.F.R. § 1.192, applicants appeal the final rejection of the pending claims of this application. The pending claims were finally rejected under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103(a) in the final Office Action of February 26, 2003. A Notice of Appeal was timely filed on May 19, 2003. This appeal brief is accompanied by the fee for a two-month extension of time.

REAL PARTY IN INTEREST:

The real party in interest for this brief is Allergy Therapeutics Limited, by way of an assignment from the inventors to Allergy Therapeutics Limited, recorded with the Office at Reel 010448, Frame 0312, on December 13, 1999.

RELATED APPEALS AND INTERFERENCES:

There are no related appeals and interferences for this matter.

STATUS OF CLAIMS:

Claims 1, 2, 6-8 and 15-23 are pending and are appealed herein. The claims stand finally rejected as follows:

1. claims 1, 2, 6-8 and 15-23 under 35 U.S.C. § 112, first paragraph as lacking an adequate written description;
2. claims 1-2, 6-8, 15-17, and 19-23 under 35 U.S.C. § 103(a) as obvious over WO 96/34626 in view of WO 92/16556, and U.S. Patent No. 5,795,862;
3. claim 18 under 35 U.S.C. § 103(a) as obvious over WO 96/34626 in view of WO 92/16556 and U.S. Patent No. 5,795,862 as applied to claims 1-2, 6-8, 15-17, and 19-23 and further in view of Marsh; WO 92/16556; U.S. Patent No. 5,750,110; and Hoyne et al.;
4. and claims 1 and 23 under 35 U.S.C. § 103(a) as obvious over WO 96/34626 in view of Holen et al.; WO 92/16556; U.S. Patent No. 5,750,110; and Hoyne et al.

STATUS OF AMENDMENTS:

No claim amendments were submitted after final rejection.

SUMMARY OF THE INVENTION:

The present invention was first described in PCT application WO 98/44947; this PCT application was filed on April 3, 1998, claiming international priority back to April 5, 1997, based upon GB 9706957.9, and published on October 15, 1998. At the time the invention was made, the inventors, Jorj Terry Ulrich and Alan Worland Wheeler were under an obligation to SmithKline Beecham and consequently, the priority document, WO 98/44947 was assigned to SmithKline Beecham. The instant U.S. patent application was filed on December 19, 1999. At the time the instant U.S. application was filed, the inventors were no longer under an obligation to SmithKline Beecham and consequently, the inventors assigned their interest in the U.S. application to Allergy Therapeutics Ltd., the latter having acquired SmithKline Beecham's rights in the invention that is the subject matter of this application on or about June 1998.

In general, the present invention relates to novel formulations for use in desensitization therapy of allergy suffers (spec. p.1, ll.3-4). Desensitization therapy results in a changed immunological response specific for a particular allergen such that the symptoms of the allergy from the allergen are ameliorated (spec. p.1, ll.5-7). Traditionally, the changed immunological response was associated with an increase in allergen specific antibodies; however, the present invention is premised on the theory that the more important immunological change in an allergic response concerns allergen specific T lymphocytes (spec. p.1, ll.6-11). Specifically, of the two subclasses of T lymphocytes, Th_1 and Th_2, it is believed that Th_2 activity is increased in an allergic subject and that this increase leads to an increase in two important components of the allergic syndrome: high allergen specific IgE antibody level and greater eosinophil

activity (spec. p.1, ll.12-16). The present invention is premised on the theory that when there is greater allergen specific Th_1 over Th_2 activity, immunotherapy of an allergic patient is improved (spec. p.1, ll.17-19). One substance that can enhance Th_1 over Th_2 in the blood of an allergic patient is 3-de-O-acylated monophosphoryl lipid A (3-DMPL) (spec. p.1, ll.26-31).

Amongst this background, the claimed invention relates to a pharmaceutical composition capable of selectively enhancing a Th_1 response over a Th_2 response, comprising tyrosine, an allergen or allergen extract, and 3-DMPL (spec. p.1, ll.32-33; claim 1). Within the context of the claimed invention, the allergen or allergen extract is coated with and/or adsorbed into tyrosine (spec. p.1, ll.33-34; claims 2 and 6-8).

The allergen of the claimed invention may be optionally modified through reaction with a cross-linking agent such as a dialdehyde or more particularly, a glutaraldehyde (spec. p.2, ll.15-16; claims 15-18). When a cross-linking agent is used, the allergen is typically modified by treatment with the cross-linking agent in an aqueous solution at a pH of between 5 and 10 and temperatures between 0°C and 100°C for up to ten hours (spec. p.2, ll.24-28). In one embodiment, the allergen may be modified at a pH of 7 and a temperature between 4°C and 37°C (such as room temperature) for approximately two hours (spec. p.2, ll.26-28). If glutaraldehyde is used as the cross-linking agent, it will typically be in the range of 50:1 to 2:1, with a preferred range of 10:1 (spec. p.2, ll.28-29).

To adsorb the allergen, the claimed invention uses tyrosine. The tyrosine is added to the allergen by mixing a solution of modified or unmodified allergen with a solution of tyrosine in a strong aqueous solution, such as hydrochloride or another inorganic acid (spec. p.2, ll.31-34; p.3, l.16). The solution of allergen typically contains between 0.1 μg/mL and 1000 μg/mL allergen protein with the ratio of allergen to tyrosine in the range of approximately $1:4 \times 10^5$ to $1:1 \times 10^2$ w/w (spec. p.2, ll.34-37). In conjunction with adding the acidic tyrosine solution to the allergen, the mixture of the allergen, the mixture is neutralized with an appropriate base and if necessary, a buffering agent (spec. p.3, ll.1-7). Neutralization is typically between pH 4.0 to no higher than pH 7.5, with a pH of 6.5 to 7.5 being most common for many allergens (spec., p.3, ll.2 and12-14). The result of the neutralization is the immediate precipitation of the tyrosine and the occlusion or adsorption of the allergen (spec. p.3, ll.15-16). The resulting precipitate is removed from the solution by centrifugation or filtration and then washed with a solution of, for example, phenol-saline before being resuspended in a physiologically acceptable carrier such as phenol-saline or water to produce an injectable composition suitable for use in desensitization therapy in combination with 3-DMPL (spec. p.3, ll.19-22).

The allergen of the claimed invention may be derived from any allergy causing substance or source, alone or in combination; such substances or sources include, for example, pollen (e.g., ragweed or

birch pollen), food, insect venom, mold, animal fur, or house dust mite (*D. farinae* or *D. pteronyssinus*) (spec. p.2, ll.9-12; claims 19-23).

THE CITED REFERENCES:

1. WO 96/34626

WO 96/34626 teaches a pharmaceutical composition that includes tyrosine and a modified allergen or allergen extract such as glutaraldehyde treated (polymerized) ragweed, birch pollen, food, mold, or house dust mite derived from *D. farinae* or *D. pteronyssinus*. This reference does ***not*** teach or suggest including 3-DMPL or any other adjuvant in the disclosed pharmaceutical composition.

2. WO 92/16556

WO 92/16556 teaches an HIV/AIDS vaccine formulation consisting of a viral antigen (a single glycoprotein of 160 Kd) with the addition of 3-DMPL. The use of the 3-DMPL in this reference is disclosed as an adjuvant to "present immunogens effectively to the host immune system such that both arms of the immune response (neutralising (sic) antibody and effector cell mediated immunity (DHT)) are produced" (p.8, ll.22-26). This reference does ***not*** teach or suggest the use of tyrosine in the disclosed formulation. Further, as is self-evident, this reference teaches antiviral immunotherapy ***not*** allergy immunotherapy.

3. U.S. PATENT NO. 5,795,862 (THE '862 PATENT)

U.S. Patent No. 5,795,862 teaches a formulation and method for isolating ectoparasite saliva proteins and a composition for detecting allergic dermatitis in an animal (col. 1, ll.15-17). At col. 42, l.32, the composition of the '862 Patent is disclosed as including "Ribi adjuvant," which may serve as a carrier to enhance the immune response of an animal to a specific antigen (col. 42, ll.19-25); however, there is ***no*** indication in this document that "Ribi adjuvant" is 3-DMPL. Further, the reference does ***not*** teach or suggest the use of tyrosine in the disclosed composition.

4. MARSH

"Preparation and Properties of 'Allergoids' Derived from Native Pollen Allergens by Mild Formalin Treatment" *Int. Arch. Allergy* 41:199-215 (1971)

Marsh is a paper that describes the production and properties of a new type of allergen derivative, termed an allergoid (p.199, ¶ 4 to p.200). For allergens, Marsh's system uses highly purified rye grass pollen antigen (p.200, ¶ 1). The allergoid of Marsh is prepared by incubating the allergoid with dilute

formaldehyde in the presence or absence of additives that become incorporated chemically into the resultant derivatives (p.201, ¶ 1). Without additives, methylene bridge linkages of varying stabilities are formed between amino and reactive aromatic residues on the allergen (such as amido or guanidine). With additives, the reactions involve cross-linkage between additive and allergen rather than intra-protein cross-linkage (p.200, ¶ 2). Due to the functional groups affected by formaldehyde modification, Marsh provides that formalinized allergens are considerably more acidic than native allergen (p.202, ¶ 1).

Marsh studied the residual allergenicities of two formalinized (32-day) derivatives (the normal and lysine allergoids) relative to native allergen by direct intradermal skin tests on grass pollen-allergic individuals (p.202, ¶ 4; Table 1). From this data, Marsh concluded that the two derivatives appeared to possess 0.01% to 0.5% of the allergenic activity of the native allergen (p.202, ¶ 4).

Marsh does ***not*** teach or suggest the use of 3-DMPL as an adjuvant for the allergoids or tyrosine to coat or adsorb the allergoids.

5. U.S. PATENT NO. 5,750,110 (THE '110 PATENT)

U.S. Patent No. 5,750,110 teaches a vaccine formulation that includes 3-DMPL and QS21 (a saponin derivative) for the treatment of infectious diseases and cancer (col. 1, ll.56-57). The '110 Patent discloses that the combination of 3-DMPL and QS21 synergistically enhance immune responses to a given antigen (col. 1, ll.20-22). The actual role that the 3-DMPL plays in enhancing the immune system is not specified. In addition, this reference does ***not*** teach or suggest the use of tyrosine in the disclosed formulation.

6. HOYNE ET AL.

"Peptide-Mediated Regulation of the Allergic Immune Response,"
***Immunology and Cell Biology* 74:180-186 (1996)**

Hoyne et al. is a review paper that examines *inter alia,* the possibility of reprogramming immune responses by promoting Th_1 responses instead of Th_2 responses (Abstract). In the introduction of this paper, Hoyne et al. explain that in a *murine* model, cytokines secreted by activated CD4+ T cells influence the nature of immune responses made to foreign antigens and in so doing, notes that Th_1 cells preferentially secrete IL-2, IFN-γ, and TNF-β, and participate in delayed-type hypersensitivity responses whereas Th_2 cells are more efficient in promoting humoral immune responses by secreting IL-4, IL-5, and IL-6, which promote the growth and differentiation of B cells and induce isotype class switching towards IgG1 and IgE. Hoyne et al. further explain that the cytokines secreted by each subset are mutually antagonistic, for example, IFN-γ secreted by Th_1 cells may inhibit the growth and differentiation of Th_2 cells, and IL-4 and IL-10 secreted by Th_2 cells can prevent the activation and growth of Th_1 cells. (*See,*

p.180, col. 1, ¶ 1.) Hoyne et al. distinguish the human model from the murine model by noting that unlike their murine counterparts, human CD4+ T cells in general do ***not*** display such polarized patterns of cytokine secretion; rather, in humans, Th_1(IFN-γ^+)-dominant or Th_2(IL-4γ^+)-dominant phenotypes have been frequently observed in certain disease states (p.180, col. 1, ¶ 2). For example, Hoyne et al. note that allergen-specific T cells isolated from atopic patients show an IL-4^{hi}/IFN-γ^{lo} (Th_2) phenotype and that these cells can support the production of antigen-specific IgE *in vitro* whereas T cells from non-atopic patients cannot induce IgE synthesis and display an IFN-γ^{hi}/IL-4^{lo} phenotype (p.180, col. 1, ¶ 2 to col. 2). Accordingly, Hoyne et al. conclude that a predominance of Th_2-like cells during an allergic response may provide the stimulus to drive and maintain a persistent allergen-specific IgE antibody response *in vivo* (p.180, col. 2).

With respect to clinical desensitization of human subjects with allergen extracts, Hoyne et al. note that success has been variable and that one of the problems is the potential variation in the level of different antigenic components in the extracts, and the presence of variant isoforms of allergens (p.183, col. 1, ¶ 1). Thus, explain Hoyne et al., for multideterminate allergens like house dust mite allergy, some antigenic components may not be in significant levels in order to achieve clinical desensitization. Hoyne et al. add that another problem posed by the use of native allergen extracts is the risk of anaphylaxis, and thus allergen-derived peptides that are recognized by specific CD4+ T cells may be of potential benefit in the long term (p.183, col. 1, ¶ 1). Hoyne et al. report that patients that have been desensitized normally display a decrease in Th_2 cytokine production and clinical improvement usually correlates with a decrease in immediate and late phase skin reactivity with a long-term rise in IgG levels, particularly IgG_4, and a decrease in specific IgE (p.183, col. 1, ¶ 2).

With respect to reprogramming the immune response, Hoyne et al. provide that successful immunotherapy may depend on altering the qualitative nature of the Th cell response in allergic patients. For example, reprogramming the immune system could be achieved by co-administering allergen in the presence of IL-12 or IFN-γ, or by immunizing with recombinant live vaccine vectors such as mycobacteria expressing defined allergens or fragments (p.183, col. 2, ¶ 2). Hoyne et al. conclude that the development of peripheral tolerance memory Th_2 cells *in vivo* has been controversial and little is known about the plasticity of the human peripheral repertoire following desensitization. Noting that it is much easier to manipulate the effector function of naïve cells rather than memory T cells and that allergic sensitization frequently occurs during infancy or early childhood, Hoyne et al. suggest that it may be beneficial to target naïve cells by vaccinating children who are at high risk of developing an allergic disease due to family history of allergy. Hoyne et al. postulate that vaccination could either induce peripheral tolerance or induce allergen-specific Th_1-type responses.

Hoyne et al. does ***not*** teach or suggest the use of tyrosine or 3-DMPL as compounds useful for regulation of the allergic immune response.

7. HOLEN ET AL.

"Specific T Cell Lines for Ovalbumin, Ovomucoid, Lysozyme and Two OA Specific Epitopes, Generated from Egg Allergic Patients' PBMC" ***Clin. Exp. Allergy*** **26(9):1080-1088 (1996) (Abstract)**

Holen et al. is a scientific paper that describes a study wherein peripheral blood mononuclear cells from hen egg allergic patients were investigated to determine the T cell epitopes responsible for the allergic response in the patients. Using various allergens of hen egg white for stimulation, long term cultures of enriched CD4+/CD8+ T cells (CD2+ > 95%) were prepared following primary proliferation responses. The long term cultures were observed for specificity, phenotype, cytokine profile, and IgE production. The allergen specific T cell lines were mapped using a panel of 13 synthetic peptides of ovalbumin. The study found that human T cells recognize ovomucoid, lysozyme, and ovalbumin epitope 105-122. It was found that ovomucoid and ovalbumin induced IgE synthesis by a small fraction (less than 1%) of B cells present in the ovomucoid and ovalbumin specific T cell lines. It was also observed that the two synthetic peptides, OA peptides 105-122 and 323-339, had no affinity to the specific IgE of the two patients.

Holen et al. does ***not*** teach or suggest the use of tyrosine or 3-DMPL as compounds useful for regulation of the T-cell response to the hen egg white allergens.

ISSUES ON APPEAL:

The following issues are to be considered on appeal:

I. Whether claims 1, 2, 6-8 and 15-23 are unpatentable as not satisfying the written description requirement of 35 U.S.C. § 112, first paragraph.

II. Whether the Examiner's primary reference, WO 96/34626, is disqualified as prior art under 35 U.S.C. § 103(a).

III. Whether the following obviousness rejections under 35 U.S.C. § 103(a) are valid:

A. claims 1-2, 6-8, 15-17, and 19-23 over WO 92/16556, and U.S. Patent No. 5,795,862 (the primary reference, WO 96/34626, being disqualified as prior art);

B. claim 18 over WO 92/16556 and U.S. Patent No. 5,795,862 as applied to claims 1-2, 6-8, 15-17, and 19-23 and further in view of Marsh, U.S. Patent No.

5,750,110, and Hoyne et al. (the primary reference, WO 96/34626, being disqualified as prior art); and

C. claims 1 and 23 over Holen et al., WO 92/16556, U.S. Patent No. 5,750,110, and Hoyne et al. (the primary reference, WO 96/34626, being disqualified as prior art).

GROUPING OF CLAIMS:

All claims stand and fall together for purposes of this appeal.

ARGUMENT:

I. THE WRITTEN DESCRIPTION REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. THE LEGAL STANDARD FOR THE WRITTEN DESCRIPTION REQUIREMENT

35 U.S.C. § 112, first paragraph reads as follows:

> *The specification shall contain a written description of the invention,* and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Since its inception in 1982, the Court of Appeals for the Federal Circuit ("Federal Circuit" or "Court") has provided a great deal of helpful guidance on interpreting the written description requirement of 35 U.S.C. § 112, first paragraph. For example, the Federal Circuit has held that what is well known in the art need not be described in detail in the specification. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). Furthermore, the Federal Circuit has stated that "[i]t is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be sufficiently clear that persons of skill in the art will recognize that the applicant made the invention having those limitations." *Martin v. Mayer,* 823 F.2d 500, 3 USPQ2d 1333 (Fed. Cir. 1987). In the important recent decision, *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* which will be explained in detail below, the Federal Circuit explained that the "purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to 'recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.'" 314

F.3d 1313, 65 USPQ2d 1385, 1386 (Fed. Cir. 2003), quoting, *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

On December 21, 1999, the Office issued the Written Description Guidelines of 64 Fed. Reg. 71427 *et seq.*, and on January 5, 2001, the Written Description Guidelines were updated at 66 Fed. Reg. 1099-1111 ("Guidelines"). At MPEP § 2163, the Office provides an overview of the Guidelines designed to assist Examiners in preparing rejections based upon the written description requirement of 35 U.S.C. § 112, first paragraph, (*see,* MPEP § 2163, pp.2100-158 to 2100-177). At the very beginning of this section of the MPEP, the Office notes an important concept, which must not be forgotten by the Examiners, it is:

> The Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. They are designed to assist Office personnel in analyzing claimed subject matter for compliance with substantive law. Rejections will be based upon the substantive law, and it is these rejections which are appealable. MPEP § 2163, p.2100-158, col. 2, 2nd para. under the primary heading.

The MPEP goes on to explain what the written description analysis requires with the following language:

> The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. MPEP § 2163, p.2100-164, middle of the col. 2 under subheading "2".

With respect to claims drawn to a genus, the MPEP provides the following guidance:

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus. MPEP § 2163, p.2100-168, col. 2, 2nd para. under subheading "ii", citing, *inter alia, In re Herschler,* 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (Disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds.").

Accordingly, under the written description requirement of 35 U.S.C. § 112, first paragraph, genus claims will be considered sufficiently described if they are fully supported by the disclosure in the specification and if one of ordinary skill in the art would understand that the inventor was in possession of the of common features of the elements possessed by the members of the genus in view of the species

disclosed. *See, e.g., University of California v. Eli Lilly,* 119 F.3d 1559, 1568, 43 USPQ2d 1389, 1406 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089 (1998).

In *Eli Lilly,* the University of California sued Eli Lilly for infringement of two of its patents. The Federal Circuit affirmed the district court's findings that the claims were invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. The invention at issue was a new recombinant human cDNA for insulin, which was claimed specifically in claim 5 and generically in claims 1 and 2, respectively, as cDNA encoding vertebrate insulin and mammalian insulin. *Eli Lilly* 43 USPQ2d at 1405. In the specification of the University of California patents, general procedures were described for isolating the cDNA but no sequence information was provided for the cDNA encoding human insulin. *Id.* The Court explained that the name "cDNA" is not itself a written description of that DNA because the word "cDNA" conveys no distinguishing information concerning its identity. *Id.* Further, the Court noted that an example that describes a method of preparing a human cDNA or a method of describing a protein that a human cDNA encodes does not necessarily describe the human cDNA itself because it provides no sequence information indicating which *nucleotides constitute human cDNA*. *Id.* By contrast, the Court noted that because the example incorporated from the parent application for rat cDNA did include nucleotide information indicating which nucleotides constitute rat cDNA, the incorporated disclosure was sufficient to describe rat cDNA. *Id.* Based upon this reasoning, the Court held that the University of California patents did not providing a written description of the human cDNA of claim 5. *Id.* With respect to the generic claims, the Court held that because the rat species was not necessarily representative of the entire genus, generic claims 1 and 2 were invalid as well. *Id.* In support of this holding, the Court provided the following explanation:

> A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by *structure, formula, [or] chemical name,*' of the claimed subject matter sufficient to distinguish it from other materials. *Id.,* citing, *Fiers v. Revel,* 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (emphasis added here).

In support of this holding, the Court also provided the following quote from *In re Smythe*:

> "In other cases, particularly, but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus..." *Eli Lilly,* 43 USPQ2d at 1405, quoting, *In re Smythe,* 480 F.2d 1376, 1383, 178 USPQ 279, 284-285 (CCPA 1973).

Lastly, the Court explained why *claims directed to genetic materials* may require the recitation of additional species when compared to claims not directed to genetic material with the following statement:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by *function...A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is*...Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. *Eli Lilly,* 43 USPQ2d at 1406 (emphasis added here).

In two important post-*Eli Lilly* cases, the Federal Circuit distinguished the holding in *Eli Lilly* and in so doing, emphasized that unlike the enablement requirement of 35 U.S.C. § 112, first paragraph, which is a question of law, the written description requirement of 35 U.S.C. § 112, first paragraph, is a *question of fact* that is analyzed on a case-by-case basis. *Enzo Biochem Inc. v. Gen-Probe Inc.,* 296 F.2d 1316, 63 USPQ2d 1609, 1612 (Fed. Cir. 2002); *Amgen,* 65 USPQ2d at 1397, citing, *Enzo, supra.*

In *Enzo,* the plaintiff, Enzo, sued several companies for infringement of its patent (U.S. Patent No. 4,900,659; "the '659 Patent") directed to nucleic acid probes that selectively hybridize to the genetic material of the bacteria that grows gonorrhea, *N. gonorrhoeae. Enzo,* 63 USPQ2d at 1610. Because *N. gonorrhoeae* has 80-93% homology with *N. meningitides,* Enzo recognized the need for a chromosomal DNA probe specific to *N. gonorrhoeae,* and consequently, it derived three such sequences that preferentially hybridize to six common strains of *N. gonorrhoeae* over six common strains of *N. meningitides. Id.* The inventors believed that if the preferential hybridization ratio of *N. gonorrhoeae* to *N. meningitidis* were greater than about five to one, then the discrete nucleotide sequence would hybridize to all strains of *N. gonorrhoeae* and to no strain of *N. meningitides. Id.* As the three derived sequences had a selective hybridization ratio of greater than fifty, these three sequences, which were in the form of a recombinant DNA molecule within an *E. coli* bacterial host, were deposited with the American Type Culture Collection (ATCC). *Id.* Generic claim 1 of the '659 Patent recites in pertinent part:

> A composition of matter that is specific for *N. gonorrhoeae* comprising at least one nucleotide sequence for which the ratio of the amount of said sequence which hybridizes to chromosomal DNA of *N. gonorrhoeae* to the amount of said sequence which hybridizes to chromosomal DNA of *N. meningitidis* is greater than about five...

The ATCC numbers of the deposited sequences were set forth in independent species claim 4.

As a defense to the suit for infringement, the defendants argued that the claims did not satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, because the patent described the claimed nucleotide sequences only by their *function* and that the deposited sequences did not cure the failure of the inventors to identify the sequences by some distinguishing characteristic, such as their *structure*. *Id.* at 1612. As support of their defense, the defendants relied upon *Eli Lilly*.

Since *Eli Lilly* was the central precedential case upon which *Enzo* would be decided, the Court explained its holding in *Eli Lilly* with the following statement:

> In *Eli Lilly*, we concluded that a claim to a microorganism containing a human insulin cDNA was not adequately described by a statement that the invention included human insulin cDNA. [Citations omitted.] The recitation of the term human insulin cDNA conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. [Citation omitted.] *We stated that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention,"* and that none of those descriptions appeared in that patent. [Citations omitted.] The specification in the *Eli Lilly* case thus did not show that the inventors had possession of human insulin cDNA. *Enzo*, 63 USPQ2d at 1613 (emphasis added here).

The Enzo Court then cautioned that "[i]t is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." Id. at 1613. In support of this statement, the Court referred to the Guidelines, cited *supra* (see p.9 of this brief), and the Office's Synopsis of Written Description Guidelines, the latter available at http://www.uspto.gov/web/patents/guides.htm ("Application Guidelines"). In its reference to the Guidelines, the Court emphasized that like the MPEP, the Guidelines are ***not*** binding on the Court but are given judicial notice to the extent that they do not conflict with the statute. *Enzo*, 63 USPQ2d at 1613. Referring to the Application Guidelines, the Court noted that the Office has acknowledged that a claim reciting *"an isolated antibody capable of binding to antigen X"* would find compliance with 35 U.S.C. § 112, first paragraph, *notwithstanding the functional definition of the antibody,* for the following three reasons:

(i) the well defined structural characteristics for the five classes of antibody;
(ii) the functional characteristics of antibody binding; and
(iii) the fact that the antibody technology is well developed and mature.

Enzo, 63 USPQ2d at 1613, citing, the Application Guidelines at pp.59-60.

Applying the teachings in this excerpt of the Application Guidelines, the *Enzo* Court noted that "under the Guidelines, the written description requirement would be met for all of the claims of the '659 Patent if the *functional characteristics* of preferential binding to *N. gonorrhoeae* over *N. meningitidis*

were *coupled* with a *disclosed correlation between that function and a structure that is sufficiently known or disclosed.*" *Enzo,* 63 USPQ2d at 1613. Finding this application of the Guidelines reasonable, the Court adopted it and presented two questions for analysis: (1) whether Enzo's *deposits* of the claimed nucleotide sequences may constitute an adequate written description of those sequences; and (2) whether the description requirement is met for all of the claims on the basis of the *functional ability* of the claimed nucleotide sequences to hybridize to strains of *N. gonorrhoeae* that are *accessible by deposit. Id.* In response to the first question, the Court held that a reference in the specification to a deposit may satisfy the written description requirement with respect to a claimed material. *Id.* at 1614. The Court reached this conclusion by analyzing the Office procedures with respect to deposits of biological materials, which requires a deposit of material when words alone cannot sufficiently describe how to make and use the invention in a reproducible manner. *Id.*, citing, 53 Fed. Reg. 39420-39425 (Oct. 6, 1988); MPEP § 2402; and 37 C.F.R. § 1.802(b) (2001). In response to the second question, the Court held that the written description requirement would be met if, upon remand, it was found that one of ordinary skill in the art would find that the generically claimed sequences *are described by their ability to hybridize to the deposited structures. Enzo,* 63 USPQ2d at 1616.

In *Amgen,* the Federal Circuit expounded on the different holdings in the *Eli Lilly* and the *Enzo* cases with the following statement:

> We held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself – not merely a recitation of its function or a reference to a potential method for isolating it. [Citation omitted.] More recently, in *Enzo Biochem,* we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, *the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure.* [Citation omitted.] *Amgen,* 65 USPQ2d at 1398 (emphasis added here).

In *Amgen,* the plaintiff, Amgen, sued several defendants for infringement of several of its patents related to the production of erythropoietin ("EPO"), a hormone that controls the formation of red blood cells in bone marrow. *Id.* at 1385. The two generic claims at issue in *Amgen* read as follows (the relevant disputed claim terms are italicized):

> *Vertebrate cells* which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 sequences that control transcription of DNA encoding human erythropoietin (claim 1 of U.S. Patent No. 5,756,349).

> A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is *purified from mammalian cells grown in culture* (claim 1 of U.S. Patent No. 5,955,422).
>
> *Id.* at 1391.

As one defense to infringement, the defendants argued that the claims of the Amgen patents were invalid as lacking an adequate written description because they failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention. *Id.* at 1398.

The Court explained why *Eli Lilly* and *Enzo* would not apply to the facts of *Amgen* with the following carefully worded statement:

> ***Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.*** Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT (the defendants collectively) *can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell – not the human DNA itself.* This difference alone sufficiently distinguishes *Eli Lilly*, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words "vertebrate" and "mammalian" *readily 'convey distinguishing information concerning their identity' such that one of ordinary skill in the art could 'visualize or recognize the identity of the members of the genus.' Amgen,* 65 USPQ2d at 1398, quoting, *Eli Lilly,* 119 F.3d at 1567, 1568, 43 USPQ2d at 1406 (emphasis added here).

Accordingly, the *Amgen* court held that the generic claims disclosed therein were adequately described by the written description of the specification of the subject patent. *Amgen,* 65 USPQ2d at 1399-1400.

Against this detailed background of the pertinent Federal Circuit case law interpreting the written description requirement of 35 U.S.C. § 112, first paragraph, applicants will explain why the Examiner's written description requirement is not proper and must be withdrawn.

B. The Generic Claims of the Instant Application Satisfy the Written Description Requirement of 35 U.S.C. § 112, First Paragraph

Relying on the Guidelines, and in particular, the Federal Circuit's holding in *Eli Lilly,* the Examiner asserts that all the pending claims of the instant application, i.e., claims 1-2, 6-8, and 15-23, are invalid as lacking an adequate written description under 35 U.S.C. § 112, first paragraph. More

specifically, the Examiner takes issue with the ***alleged*** failure of the specification to provide a written description of the following (the Examiner's exact language and emphasis is provided):

> (1) *any* pharmaceutical composition capable of selectively enhancing a Th_1 response over a Th_2 response comprising tyrosine, *any* allergen or *any* allergen extract, and 3-DMPL;
>
> (2) *any* composition capable of selectively enhancing a Th_1 response over a Th_2 response comprising tyrosine, *any* allergen or *any* allergen extract, and 3-DMPL wherein the allergen or allergen extract is coated with and/or adsorbed onto tyrosine;
>
> (3) *any* composition capable of selectively enhancing a Th_1 response over a Th_2 response comprising tyrosine, *any* allergen or *any* allergen extract, and 3-DMPL wherein the allergen or allergen extract is coated with the tyrosine;
>
> (4) *any* composition mentioned above wherein the allergen or allergen extract is modified by reaction with any cross-linking agent such as dialdehyde or glutaraldehyde; and
>
> (5) *any* composition mentioned above wherein the allergen or allergen extract is not modified with any cross-linking agent for treating allergy.
>
> Office Action, pp.2-3, bridging paragraph.

As preliminary matters, applicants would like to note the following indiscrepancies in the Examiner's written description requirement to this Honorable Board. First, applicants submit that item (3) should be ignored as the subject matter identified therein repeats the subject matter in item (2). Second, the emphasis in the Examiner's use of the phrase "any composition" appears to take issue with the applicants' preamble language in the claims, which uses the well-established: "A pharmaceutical composition…comprising" language (*see,* Appendix A, which lists all of the pending claims for this application). Because the Examiner only presents arguments against the applicants' recitation of an "allergen" or an "allergen extract" on page 3 of the Office Action, the Examiner provides no clue as why she has used and emphasized the word "any" in the itemization. Furthermore, because applicants know of no other way to claim a pharmaceutical composition than to use the language "A pharmaceutical composition…comprising," applicants regrettably cannot do more than assert that the Examiner's issue with the use of applicants' preamble language is not proper as lacking both factual and legal support. In light of the foregoing, applicants have no choice but to limit the following discussion to the claim elements "an allergen" and "an allergen extract."

The Examiner's emphasis on *Eli Lilly* in the written description requirement is misguided for two critical reasons, they are: (i) the composition of the present invention is ***not*** directed to a novel structure as was the cDNA in *Eli Lilly*, and (ii) the composition of the present invention is ***not*** in an unpredictable art, as are the genetic materials of *Eli Lilly*. *See, Amgen, supra.*

The broadest generic claim of the instant application is claim 1, which reads as follows:

> A pharmaceutical composition capable of selectively enhancing a Th_1 response over a Th_2 response, comprising tyrosine, an allergen, or allergen extract, and 3-DMPL.

As explained immediately above, the claim elements at issue are the terms "an allergen" and "an allergen extract." Relying upon *Eli Lilly,* the Examiner asserts that these generic terms are not adequately described in the specification because not enough species are disclosed. It is the Examiner's position that the claims encompass an indefinite number of allergen and allergen extracts that are not disclosed.

In response to the Examiner's assertions, applicants present this Honorable Board with two very important points for consideration.

First, under the Examiner's rubric, generic claims would have to cease to exist in all United States patents because generic claims by their very nature are broadly worded so as to encompass undisclosed species that fall within a claim's parameters. In the instant case, it is clear that applicants disclosed a series of allergen species, namely, pollen, (e.g., ragweed or birch pollen), food, insect venom, mold, animal fur, or house dust mite (*D. farinae* or *D. pteronyssinus)* (spec. p.2, ll.9-11). Regardless of this exemplary disclosure, the Examiner maintains that not enough species are disclosed to describe the allergen genus (*see,* Office Action, p.4). Despite the obviousness of the error in the Examiner's assertion from a factual standpoint, the second point detailed below will reveal that the Examiner's incorrect conclusion was derived from a misplaced reliance on *Eli Lilly.*

The second point for the Board's consideration is applicants' assertion that it is the *Amgen* holding and ***not*** the *Eli Lilly* holding that governs the written description requirement for this case. As explained by the *Amgen* Court, *Eli Lilly* only applies where the structure at issue is novel and in an unpredictable art. In *Eli Lilly,* the claimed cDNA was a novel cDNA, which was defined only by its function and not by its structure. Because the Court determined that recombinant DNA technology is an unpredictable art, the Court could only conclude that the one of ordinary skill in the art could not determine the claimed cDNA without information relating to its structure. By contrast, in *Enzo,* the generically claimed genetic materials, while arguably also in an unpredictable art, were found to be adequately described by the ATCC deposit of the disclosed species. In contrast to both *Eli Lilly* and *Enzo,* the *Amgen* decision, which is directly on point in this case, holds that *Eli Lilly* and *Enzo* are ***not*** applicable where the claims terms at issue are ***not new or unknown biological materials that ordinary artisans would easily miscomprehend.*** Accordingly, in *Amgen,* the Court was satisfied with a generic recitation of "vertebrate" and "mammalian" cells. As support for its holding, the *Amgen* Court expressly referenced the Application Guidelines promulgated by the Office and in so doing, noted that the Office

would consider a generic recitation of an antibody as a known art not requiring disclosure of more than one or a few species.

Similarly, in the instant application, the generic recitation of "allergens" and "allergen extracts" would also constitute well-known biological materials that ordinary artisans would readily comprehend. Indeed, the list of exemplary allergens set forth in the specification of the instant application is not a list of allergens that would not be known to many an allergy sufferer; to wit, the list includes such well-known allergens as pollen (e.g., ragweed or birch pollen), food, insect venom, mold, animal fur, or house dust mite (*D. farinae* or *D. pteronyssinus*). Because allergen extracts are routinely acquired through purification of allergens by way of dialysis or fractionation (*see,* spec. p.4, "Preparation 1"), it follows that an allergen extract may be derived from any allergen. With respect to the inclusion of peptides containing one or more epitopes of an allergen within the definition of "allergens" (*see,* spec. p.2, ll.12-14 and p.2 of the Office Action) and the recitation of modified allergens (claim 15), a review of the references submitted in the PTO-1449 and PTO-892 forms for this application will readily show that the production of such peptides and the modification of allergens and allergen extracts are procedures well-known by those versed in the art of allergy treatment. *See, e.g.,* Marsh et al. (1970) and Marsh (1971), whose "allergoids" are essentially modified allergens (cited in the Amendment of Oct. 5, 2001, and the Office Action of Feb. 26, 2003); Patterson et al. (1973(2) and 1974), which disclose both allergen fragments and allergen modification through cross-linking (cited in the Amendment of Oct. 5, 2001, and the Office Action of Feb. 26, 2003); U.S. Patent No. 1,377,074 (1971), which discloses allergen extracts, and U.S. Patent No. 1,492,973 (1974), which discloses chemical modification of allergens and allergen extracts (PTO-1449 of October 1, 1999); Wheeler et al. (1976) and Moran et al. (1977), both which disclose chemical modification of grass pollen extracts (cited in the Amendment of Oct. 5, 2001, and the Office Action of Feb. 26, 2003); Holen et al. (1996), which discloses synthetic peptides to egg white allergens (PTO-892 of Feb. 26, 2003); and Hoyne et al. (1996), which discloses allergen peptides containing immunodominant epitopes (PTO-892 of Feb. 26, 2003).[1]

As the foregoing demonstrates, the subject matter of the claimed invention is in a well-established art; accordingly, *the exemplary species identified by applicants in the specification are sufficient to alert*

[1] Applicants note that the Marsh, Marsh et al., Patterson et al. (3), Wheeler et al., and Moran et al. references were cited and provided in the Amendment of October 5, 2001, not as relevant art but merely as art showing that the term "modified" as applied to the term "allergen" has been readily understood by those of ordinary skill in the art for more than 20 years (Amendment of October 5, 2001, pp.4-5). These references were ***not*** submitted in a PTO-1449 because applicants were of the opinion at the time and remain of the opinion that these references are ***not*** relevant to the present invention but merely informative as background art. In the Office Action of February 26, 2003 (p.8, para. 10), the Examiner cites the Marsh reference and in so doing, indicates that this reference was submitted by the applicants in a PTO-1449. Applicants note to this Honorable Board that this is not true. The Marsh reference cited in the Office Action of February 26, 2003, was never cited in either a PTO-1449 or a PTO-892.

the ordinary artisan to the scope of the claimed invention. See, e.g., MPEP § 2163, citing, *In re Herschler, supra* (quoted on page 8 of this brief); and *Amgen, supra* (quoted on page 13 of this brief). Further on the issue of the subject matter of the claimed invention, applicants take this opportunity to note that the novelty of the claimed invention relates not to the claimed allergens, allergen extracts, allergen-derived peptides, or modified allergens, but rather, to the *novel pharmaceutical composition that results when the recited allergen and allergen extracts are combined with tyrosine and 3-DMLP such that a* Th_1 *response is selectively enhanced over a* Th_2 *response* (as recited in claim 1).

As a final matter, applicants note that because the Guidelines were prepared for publication on January 5, 2001, the analysis disclosed therein is limited to only to case law that was available as of the publication date. Accordingly, while the Examiner's sole reliance on the Guidelines is understandable, it is evident from the analysis provided herein, that the Examiner's reliance on the Guidelines resulted in a disregard of important subsequent case law that explains and overrides the case law and analyses that were available as of January 5, 2001. Because the Guidelines cannot trump the law (*see, e.g.,* MPEP § 2163 referenced on page 8 of this brief) applicants submit that the Examiner's reliance on the Guidelines is improper because is ignores pertinent and applicable Federal Circuit law published subsequent to January 5, 2001. Because ***Amgen is the case on point*** with respect to adequacy of the generic claims of this patent application and ***Eli Lilly does not apply*** to the claims at issue, applicants respectfully request reversal of the Examiner's rejection of claims 1, 2, 6-8, and 15-23 as unpatentable for failure to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

II. THE OBVIOUSNESS REJECTIONS

A. THE LEGAL STANDARD FOR OBVIOUSNESS

The *prima facie* case is a procedural tool which, as used in patent examination, means not only that the evidence of the prior art would reasonably allow the conclusion the Examiner seeks, but also that the prior art compels such a conclusion if the applicant produces no evidence or argument to rebut it. *In re Spada,* 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990). To establish a *prima facie* case of obviousness, three criteria must be met: first, the prior art reference must teach or suggest the desirability of the claimed combination; second, the Office must show that the ordinary artisan would be motivated to modify the reference or to combine the reference teachings; and third, there must be a showing that the ordinary artisan would have a reasonable expectation of success at arriving at the claimed combination based *solely* on the teachings of the cited prior art reference. *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453 (Fed. Cir. 1998); *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Deminski,* 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986).

B. THE PRESENT INVENTION PREDATES THE PRIMARY WO 96/34626 REFERENCE, THUS, WO 96/34626 IS DISQUALIFIED AS PRIOR ART UNDER 35 U.S.C. § 103(a)

The Examiner's obviousness rejection is set forth under 35 U.S.C. § 103(a), which reads as follows:

> 35 U.S.C. § 103:
>
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The primary reference in the Examiner's obviousness rejection is the WO 96/34626 reference, which has international publication date of November 7, 1996, and an international filing date of April 25, 1996. Pursuant to 35 U.S.C. § 102(a), the effective date of the WO 96/34626 reference is its international publication date. Accordingly, under 35 U.S.C. § 103(a), proof of invention prior to the effective date of the WO 96/34626 reference will serve to disqualify this reference as prior art to the instant application. At 37 C.F.R. § 1.131, the rules for predating an invention behind a cited reference are set forth with the following language, which is provided in pertinent part:

> 37 C.F.R. § 1.131:
>
> (a) When any claim of an application...is rejected, the inventor of the subject matter of the rejected claim...may submit an appropriate oath or declaration to establish the invention of the subject matter of the rejected claim prior to the *effective date* of the reference or activity on which the rejection is based. The effective date of...[an] international application publication under PCT Article 21(2) is the earlier of its publication date or date that it is effective as a reference under 35 U.S.C. § 102(e). Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country.
>
> (b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. Original exhibits of drawings or records, or photocopies thereof, must accompany and form part of the affidavit or declaration or their absence satisfactorily explained.

The attached Declaration of Alan Worland Wheeler ("Wheeler Declaration") demonstrates that the subject matter of the claimed invention predates the November 7, 1996, filing date of the WO

96/34626 reference (Wheeler Declaration, paras. 7-9). Attached to the Wheeler Declaration is a letter from Dr. Wheeler forwarding a draft of the priority document of the instant application (the application that would be filed as the WO 98/44847 priority document) to Dr. Terry Ulrich, the coinventor of the present invention, for Dr. Ulrich's review (Wheeler Declaration, Exh. A). Although the date of the letter is redacted, Dr. Wheeler swears in his Declaration that the date on this letter is prior to the November 7, 1996, publication date of the WO 96/34626 reference (Wheeler Declaration, para. 8). With Dr. Wheeler's proof that the claimed invention predates the November 7, 1996, effective date of the WO 96/34626 reference, the WO 96/34626 reference no longer qualifies as prior art under 35 U.S.C. § 103(a).

On a separate but related matter, applicants submit that pursuant to the current statutory scheme of 35 U.S.C. §§ 102(e) and 103(c), the WO 96/34626 reference would be disqualified as prior art to the instant application because the WO 96/34626 reference (i) designates the United States (35 U.S.C. § 102(e)) and (ii) SmithKline Beecham PLC owned both the WO 96/34626 reference and the subject matter of the instant application at the time the claimed invention was made (35 U.S.C. § 103(c)). The current version of 35 U.S.C. § 102(e) reads as follows:

> 35 U.S.C. § 102
>
> A person shall be entitled to a patent unless —
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

In the "1999 Note" following 35 U.S.C. § 102, it is provided that this version of the statute only applies to those applications that were filed after November 29, 2000. For those applications filed prior to November 29, 2000, the prior version of the statute applies, it reads as follows:

> 35 U.S.C. § 102:
>
> A person shall be entitled to a patent unless —
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

When either the current or the prior version of 35 U.S.C. § 102(e) is read in concert with 35 U.S.C. § 103(c), the end result is that any prior art that is not prior art under 35 U.S.C. §§ 102(a)-(d) may be disqualified as prior art under 35 U.S.C. § 103 if the reference and the claimed invention were commonly owned at the time the claimed invention was made. Section 103(c) of the Patent Statute reads as follows:

> 35 U.S.C. § 103:
>
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Because the WO 96/34626 reference was filed prior to November 29, 2000, the prior version of 35 U.S.C. § 102(e) controls the disqualification of this reference under 35 U.S.C. § 103(c).

Turning first to the non-qualification of the WO 96/34626 reference as prior art under 35 U.S.C. §§ 102(a)-(d), applicants note that the Wheeler Declaration demonstrates that this reference is disqualified as prior art under 35 U.S.C. § 102(a). Further, because the WO 96/34626 reference was published only five months prior to the April 5, 1997, priority date of the instant application, the WO 96/346262 reference does not serve as a statutory bar under 35 U.S.C. § 102(b). Regarding section 102(c) and 102(d) of the Patent Statute, applicants submit that these sections inapplicable to this case and thus do not apply.

Turning next to the national phase requirements set forth in the prior version of 35 U.S.C. § 102(e), applicants note that due to corporate changes at SmithKline Beecham PLC (now GlaxoSmithKline), it is impossible at this time to verify that the WO 96/34626 reference was filed in the United States as a national stage application and that the requirements of 35 U.S.C. § 371(c)(1), (2), and (4) were satisfied for the WO 96/34626 reference. On this matter, if this Honorable Board is able to verify through the official record that the WO 96/34626 reference was filed as a U.S. national phase application under 35 U.S.C. § 371(1), (2), and (4), then applicants respectfully request acknowledgment of same.

In the event that the WO 96/3426 reference was filed as a national state application, applicants submit that the Wheeler Declaration demonstrates that the WO 96/34626 reference and the claimed invention were commonly owned at the time the claimed invention was made in accordance with the provisions of 35 U.S.C. § 103(c) (Wheeler Declaration, paras. 4-6). In light of the foregoing, the following Statement Concerning Common Ownership is provided for purposes of this request:

STATEMENT CONCERNING COMMON OWNERSHIP

Applicants state WO 96/34262 and the instant application, United States Patent Application Serial No. 09/402,273, were, at the time the invention of the instant application was made, both owned by SmithKline Beecham PLC.

Accordingly, if this Honorable Board is able to verify that the WO 96/34626 reference was filed as a national stage application under 35 U.S.C. § 371(c)(1), (2), and (4), applicants respectfully request disqualification of the WO 96/34626 reference as prior art against the instant application pursuant to the effective provisions of 35 U.S.C. §§ 102(e) and 103(c).

Notwithstanding the outcome of the common ownership issue as discussed immediately above, applicants submit that the WO 96/34626 reference is nonetheless disqualified as prior art against the instant application solely on the grounds that the claimed invention predates the effective date of the WO 96/34626 reference. With the disqualification of this reference, the Examiner's obviousness rejection must stand solely on the combination of teachings from the cited secondary references. The following discussion will demonstrate why the secondary references, alone or in combination, do not teach or suggest the claimed invention.

C. THE SECONDARY REFERENCES, ALONE OR IN COMBINATION, DO NOT TEACH OR SUGGEST THE CLAIMED INVENTION

1. CLAIMS 1, 2, 6-8, 15-17, AND 19-23 ARE NOT OBVIOUS OVER WO 92/16556 AND THE '862 PATENT

With the disqualification of the primary reference, WO 96/34262, the Examiner's rejection can only stand its ground if the secondary references, alone or in combination, teach or suggest the claimed invention. As recited in independent claim 1, the claimed invention is drawn to a pharmaceutical composition capable of selectively enhancing a Th_1 response over a Th_2 response, comprising tyrosine, an allergen or allergen extract, and 3-DMPL.

WO 92/16556 teaches the use of 3-DMPL as an adjuvant useful in the treatment of Human Immunodeficiency Virus (HIV). The Examiner cites this reference on the grounds that the 3-DMPL disclosed therein is used to induce a Th_1 response. With respect to the Examiner's assertions on the purpose of the 3-DMPL in WO 92/16556, applicants note to this Honorable Board that WO 92/16556 does ***not*** teach or suggest that the 3-DMPL is being used to induce a Th_1 response; rather, as previously noted, WO 92/16556 teaches that the 3-DMPL is used as an adjuvant to "present immunogens effectively to the host immune system such that both arms of the immune response (neutralising (sic) antibody and effector cell mediated immunity (DHT)) are produced" (p.8, ll.22-26). Regardless of the purpose of the

3-DMPL, it is unarguable that because this reference is directed solely to a vaccine used for the treatment of HIV/AIDS, it follows that the disclosure of the 3-DMPL is clearly not intended for use with an allergen or allergen extract. Further, as previously mentioned, this reference does ***not*** contemplate the use of tyrosine in combination with the 3-DMPL for any purpose.

As already discussed, the '862 Patent teaches the use of a modified flea saliva protein and a Ribi adjuvant to improve the immune response of an antigen. The Examiner cites this reference on the assumption that "Ribi Adjuvant" is equivalent to 3-DMPL (*see,* Office Action, p.5, 4th para); applicants submit that this is not necessarily the case. As shown in the *Research Adjuvant Fact Sheet* from Corixa Corporation, formerly Ribi ImmunoChem (attached at Appendix B), Ribi Adjuvant is a known adjuvant for research use in polyclonal and monoclonal antibody production; it contains one of more of the following microbial components:

MPL®	Monophosphoryl Lipid A
TDM	Synthetic Trehalose Dicorynomycolate
CWS	Cell Wall Skeleton

The '862 Patent does ***not*** specify which of the three Ribi adjuvant systems is used therein. Despite the foregoing, more importantly, the '862 Patent ***fails*** to teach or suggest the use of tyrosine to coat or adsorb the flea saliva protein disclosed therein.

Because neither reference teaches or suggests the use of tyrosine, it follows that the ordinary artisan could not arrive at the claimed invention solely by reading the disclosures of WO 92/16556 and the '862 Patent. Accordingly, since the secondary references, alone or in combination do not teach or suggest the claimed invention, applicants respectfully request withdrawal of the Examiner's obviousness rejection of claims 1, 2, 6-8, 15-17, and 19-23 over WO 92/16556 and the '862 Patent (WO 96/34626 being disqualified as prior art).

2. CLAIM 18 IS NOT OBVIOUS OVER WO 92/16556 AND THE '862 PATENT AS APPLIED TO CLAIMS 1, 2, 6-8, 15-17, AND 19-23 AND FURTHER IN VIEW OF MARSH, THE '110 PATENT, AND HOYNE ET AL.[2]

Claim 18, which depends from claim 1, recites an embodiment of the claimed invention wherein the allergen extract is not modified by reaction with a cross-linking agent. Because claim 1 is not rendered obvious by the combination of WO 92/15665 and the '862 Patent (the WO 96/34626 Patent being disqualified as prior art) as set forth above, it follows that claim 18 cannot be rendered obvious by

[2] At p.8, para. 10 of the Office Action, the Examiner cites WO 92/16556 twice in the same rejection. For purposes of this appeal, applicants have omitted the second incidence of the WO 92/16556 reference.

the cited combination. Notwithstanding the foregoing and for the sake of clarity and completion, applicants will explain why the teachings of the cited references (sans WO 96/34626) do not teach or suggest the invention of claim 18.

As set forth above, WO 92/15665 and the '892 Patent fail to teach or suggest the use of tyrosine. The Examiner cites Marsh for the teaching of an unmodified native allergen. The '110 Patent is cited for another teaching of 3-DMPL; the disclosure of 3-DMPL in this reference relating solely to the synergistic effect that the 3-DMPL has with the saponin derivative QS21 in enhancing immune responses to a given antigen (col. 1, ll.20-22). As previously noted, the '110 Patent does ***not*** teach or suggest the use of tyrosine in the disclosed vaccine formulation, which is taught for the treatment of infectious diseases or cancers (col. 1, ll.56-57). Hoyne et al. is cited for the teaching that reprogramming of immune responses may be achieved by promoting a Th_1 response over a Th_2 response. While the Hoyne et al. reference provides a great deal of interesting information on the role of interleukins, interferons, cytokines, and CD4+ T cells in the murine and human immune responses, this reference fails to teach or suggest the use of tyrosine or 3-DMPL as compounds to be used in desensitization therapy.

Because none of the cited references, alone or in combination, teach or suggest the essential element of tyrosine as a component of a composition used for desensitization therapy against an unmodified allergen, it follows that claim 18 is not rendered obvious by the cited combination of references. Accordingly, applicants respectfully request that this Honorable Board reverse the Examiner's obviousness rejection of claim 18 over WO 92/16556 and the '862 Patent as applied to claims 1, 2, 6-8, and 15-17 and 19-23 and further in view of Marsh; the '110 Patent; and Hoyne et al. (WO 96/34626 being disqualified as prior art).

3. CLAIMS 1 AND 23 ARE NOT OBVIOUS OVER HOLEN ET AL., WO 92/16556, THE '110 PATENT, AND HOYNE ET AL.

Claim 23, which depends from claim 1, recites an embodiment of the claimed invention wherein the allergen or the allergen extract is selected from the group consisting of grass pollen and ovalbumin. Because claim 23 depends from claim 1, the cited references, alone or in combination must teach or suggest all of the elements of claim 1 plus the additional elements of claim 23 in order for the Examiner's obviousness rejection to stand. With the disqualification of the primary reference, WO 96/34626, the Examiner's obviousness rejection must be based solely upon the teachings of the secondary references.

The Examiner cites Holen et al. for the teaching that human T cells recognize the "food" (i.e., hen egg white) allergens: ovomucoid, lysozyme, and ovalbumin epitope 105-122. As previously noted, the Holen et al. reference fails to teach or suggest the use of tyrosine or 3-DMPL as compounds useful for regulation of the T-cell response to the hen egg white allergens. As discussed above, WO 92/16556

teaches 3-DMPL as an immune response regulator but fails to teach or suggest tyrosine as a compound useful in the modulation of immune responses. Similarly, the '110 Patent teaches the use of 3-DMPL in combination with the saponin derivative QS21 for the enhancement of an immune response to a given antigen but fails to teach or suggest the addition of tyrosine to the disclosed formulation. Lastly, the Hoyne et al. reference teaches the mechanisms involved in the immune response to certain allergens but fails to teach or suggest tyrosine or 3-DMPL as beneficial regulators of the immune response.

Because none of the cited references alone or in combination teach or suggest a combination of tyrosine, 3-DMPL, and grass pollen or ovalbumin allergens or allergen extracts, it follows that claims 1 and 23 are not rendered obvious by the cited combination of references. Accordingly, applicants respectfully request that this Honorable Board reverse the Examiner's obviousness rejection of claims 1 and 23 over Holen et al.; WO 92/16556; the '110 Patent; and Hoyne et al. (WO 96/34626 being disqualified as prior art).

CONCLUSION

With this appeal, applicants request the following actions from this Honorable Board. First, because the claimed invention satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, applicants respectfully request that this Honorable Board reverse the Examiner's written description rejection for the claims of this application. Second, applicants request that this Honorable Board acknowledge that WO 96/34626 is disqualified as prior art for this application under 35 U.S.C. § 103(a) because the date of invention of the claimed subject matter predates the effective date of the WO 96/34626 reference. Third, applicants request that this Honorable Board reverse the Examiner's obviousness rejections on the grounds that none of the qualifying cited references, alone or in combination, teach or suggest the claimed invention.

Respectfully submitted,

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APPENDIX A

CLAIMS ON APPEAL

1. **(previously amended)** A pharmaceutical composition capable of selectively enhancing a TH_1 response over a TH_2 response, comprising tyrosine, an allergen or allergen extract, and 3-DMPL.

2. **(previously amended)** A composition according to claim 1, wherein the allergen or allergen extract is coated with and/or adsorbed onto tyrosine.

6. **(previously amended)** A composition according to claim 2, wherein the allergen or allergen extract is coated with the tyrosine.

7. **(previously amended)** A composition according to claim 2, wherein the allergen or allergen extract is adsorbed onto the tyrosine.

8. **(previously amended)** A composition according to claim 2, wherein the allergen or allergen extract is coated with and adsorbed onto the tyrosine.

15. **(previously added)** A composition according to claim 1, wherein the allergen or allergen extract is modified by reaction with a cross-linking agent.

16. **(previously added)** A composition according to claim 15, wherein the cross-linking agent is a dialdehyde.

17. **(previously added)** A composition according to claim 16, wherein the dialdehyde is glutaraldehyde.

18. **(previously added)** A composition according to claim 1, wherein the allergen or the allergen extract is not modified by reaction with a cross-linking agent.

19. **(previously added)** A composition according to claim 1, wherein the allergen or the allergen extract is derived from a source selected from pollen, food, insect venom, mold, animal fur, house dust mite, and combinations thereof.

20. **(previously added)** A composition according to claim 19, wherein the allergen or the allergen extract is derived from ragweed pollen or birch pollen.

21. **(previously added)** A composition according to claim 19, wherein the allergen or allergen extract is derived from dust mite of species *D. farinae* or *D. pteryssinus*.

22. **(previously added)** A composition according to claim 19, wherein the allergen or the allergen extract is selected from the group consisting of pollen and food.

23. **(previously added)** A composition according to claim 22, wherein the allergen or the allergen extract is selected from the group consisting of grass pollen and ovalbumin.

APPENDIX B

Ribi Adjuvant System (RAS)

Research Adjuvant Fact Sheet

Corixa Corporation is proud to offer the Ribi Adjuvant System (RAS) for research applications. RAS components are derived from bacterial and mycobacterial cell walls, and are among the most potent adjuvants known. Corixa's adjuvant technology is based on decades of research that reinforces its position as a leader in adjuvant development.

DESCRIPTION

Three formulations of RAS are available for research use in polyclonal and monoclonal antibody production. RAS consists of highly purified microbial components contained in metabolizable oil, both lending to its effectiveness and low toxicity in research animal models. Each vial of adjuvant contains 0.5 mg of one or more of the following microbial components:

MPL®	Monophosphoryl Lipid A
TDM	Synthetic Trehalose Dicorynomycolate
CWS	Cell Wall Skeleton

These components are incorporated into 44 μL squalene and Polysorbate-80. Once reconstituted this non-viscous oil-in-water emulsion provides an excellent vehicle for delivery. The emulsion may act through three different functions: 1) The metabolizable oil solubilizes TDM and facilitates binding of antigen to the oil droplets; 2) The oil provides a depot of both adjuvant and antigen at the injection site; 3) Soluble antigens are rendered particulate when they adhere to the oil droplets. In this physical state antigens are more easily phagocytosed by macrophages and processed during the early stages in the initiation of an immune response.

BENEFITS

Effectiveness

RAS has been commercially available for research purposes since 1985; its potent adjuvant activity with diverse antigens and animal models is documented in numerous published studies. Data from published comparative studies are available demonstrating the potency and side effect profile. Many of the reports show the ability of RAS to induce cellular as well as humoral immune responses to various antigens including carbohydrates, peptides, microbial subunits, synthetic polypeptides, membrane proteins and DNA constructs. Antibodies generated in animals immunized with RAS are specific to the antigen of interest with little or no cross reactivity. RAS is ideal for research use in mice, guinea pigs, rats, rabbits, goats and non-human primates.

Reduced Animal Trauma

The highly purified natural and synthetic components contained in RAS are powerful adjuvants without the toxic and allergenic properties of microbial substances. Institutional animal care and use committees recommend its use to researchers.

Cost Effective

Because RAS is ready-made and non-viscous, the ease of preparation and administration reduces costly preparation time. The adjuvant is prepared simply by adding the antigen in saline and briefly vortexing. Furthermore, since RAS is widely used for research applications, most institutional animal welfare committees do not require lengthy justification reports.

RESEARCH FORMULATIONS

- **MPL + TDM Emulsion (Product Code: R-700)**
  Recommended for use in mice, guinea pigs and rats with diverse range of antigens.
- **MPL + TDM + CWS Emulsion (Product Code: R-730)**
  Recommended for use in rabbits, goats and primates with diverse range of antigens.
- **TDM Emulsion (Product Code: R-760)**
  Recommended for use in mice with immunogenic antigens.

All formulations reconstitute to 2.0 mL final volume with antigen in saline or PBS.

RECONSTITUTION

Warm the vial to 40-45°C for 5-10 minutes. Using a syringe with a 20 or 21 gauge needle, inject 2.0 mL saline solution containing desired amount of antigen directly into the vial through the rubber stopper. Vortex the vial vigorously for 2-3 minutes, leaving the cap seal and rubber stopper in place. Because oil may adhere to the rubber stopper, it is important to invert the vial during the vortexing process. Final volume of adjuvant/antigen is 2.0 mL with a concentration of 2% squalene oil. (NOTE: Antigen may be incorporated into adjuvant at a concentration of 0.05 mg – 0.25 mg per mL of saline.) If the entire contents of the vial will not be used initially, reconstitute with saline alone to 1.0 mL and mix aliquots 1:1 with antigen in saline.

RESEARCH PROTOCOLS

Small animal models:

MPL + TDM Emulsion (R-700)
TDM Emulsion (R-760)[1]

MICE		0.2 mL Dose, administered as:
		0.1 mL subcutaneous, two sites[2]
	or	0.2 mL intraperitoneal
GUINEA PIGS, RATS		0.5 mL Dose, administered as:
		0.2 mL subcutaneous, two sites
	and	0.1 mL intraperitoneal

[1]use with immunogenic antigens; [2]preferred

Inject on Day 0, boost on Day 21 and test bleed on Day 26 or 28. If necessary, booster injections may be given every 21 days, using the same formulation. For monoclonal production, boost intravenously (or intraperitoneally) with saline/antigen only 14 days after last adjuvant/antigen injection. Remove spleen for fusion three days after IV injection.

Large animal models:

MPL + TDM + CWS Emulsion (R-730)

RABBITS		1.0 mL Dose, administered as:
		0.05 mL intradermal, six sites; 0.3 mL
		intramuscular into each hind leg
	and	0.1 mL subcutaneous in neck region
GOATS		1.0 mL Dose, administer as:
		0.5 mL intramuscular into each hind leg

Inject on Day 0, boost on Day 28 and test bleed on Day 38 and 42. If necessary, booster injections may be given every 28 days, using the same formulation. (NOTE: injecting more than every 28 days may induce tolerance.)

STABILITY

RAS may be stored at 2-8°C indefinitely prior to reconstitution. Unused adjuvant/antigen emulsion may be stored at 4°C for several months, depending on nature of antigen. DO NOT FREEZE.

ADDITIONAL INFORMATION

For more information, please contact:
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Ribi Adjuvant System (RAS) formulations are for RESEARCH USE ONLY – NOT FOR HUMAN USE